TECHNOLOGY DEVELOPMENT FOR HIGH RESOLUTION ELECTRON MICROSCOPY

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National Institute of General Medical Sciences (NIGMS)
National Institute of Arthritis and Musculoskeletal Diseases (NIAMS)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

THIS PA USES THE "MODULAR GRANT" AND "JUST-IN-TIME" CONCEPTS. IT INCLUDES DETAILED MODIFICATIONS TO STANDARD APPLICATION INSTRUCTIONS THAT MUST BE USED WHEN PREPARING APPLICATIONS IN RESPONSE TO THIS PA.

PURPOSE

The goal of this Program Announcement (PA) is to promote the development of the technology of high resolution electron microscopy (EM) so that it can be applied together with complementary structural approaches for (1) routine determination of the atomic structures of isolated macromolecular assemblies and (2) the analysis of the spatial distribution of macromolecules in cells. The application of EM to a broad range of problems in molecular and cellular biology is currently supported by the National Institutes of Health (NIH) through a variety of mechanisms, and is not part of this program announcement. This PA addresses technology development.

Applications for developing technology that improves the capabilities of high resolution EM are invited. The participating institutes are especially interested in promoting cross-disciplinary collaborations with established experts in fields of engineering, physics, mathematics, computer science, chemistry, and materials science.

HEALTHY PEOPLE 2010

The Public Health Service (PHS) is committed to achieving the health promotion and disease prevention objectives of "Healthy People 2010," a PHS led national activity for setting priority areas. This PA, Technology Development for High Resolution Electron Microscopy, is related to one or more of the priority areas. Potential applicants may obtain a copy of "Healthy People 2010" at http://www.health.gov/healthypeople/.

ELIGIBILITY REQUIREMENTS

Applications may be submitted by domestic and foreign, for-profit and non-profit organizations, public and private, such as universities, colleges, hospitals, laboratories, units of State and local governments, and eligible agencies of the Federal government. Racial/ethnic minority individuals, women, and persons with disabilities are encouraged to apply as principal investigators.

The participating institutes invite participation of investigators from the physical sciences, engineering, and mathematics, especially in collaboration with established, NIH-funded investigators who are already active in the application of high resolution EM to biological problems. Collaborating investigators need not have prior experience with biological problems or the NIH, but should have skills relevant to technology development for high resolution EM and established credentials in their areas of expertise.

MECHANISM OF SUPPORT

This PA will use existing NIH research project grant (R01) and program project grant (P01) mechanisms. Investigators may also apply for the Small Business Innovation Research (SBIR; R43, R44) and Small Business Technology Transfer Research (STTR; R41, R42) award mechanisms. Applications for competing supplements to existing grants will also be accepted, if there will be at least one year remaining in the project period at the time of supplement funding. Foreign institutions are not eligible for P01, R41, R42, R43, or R44 grants. Responsibility for the planning, direction, and execution of the proposed project will be solely that of the applicant. The total project period for an application submitted in response to this PA may not exceed five years. The average duration of NIGMS R01 grant awards is four years.

The research project grant (R01) is the preferred grant mechanism for most research efforts involving one or two groups. For complex multi-investigator research efforts requiring advanced instrumentation and associated infrastructure, the program project grant (P01) may be the preferred mechanism.

Investigators planning to apply for program project grants from NIGMS should contact NIGMS staff (see INQUIRIES below) to learn about the current guidelines. For the NIGMS policy on program project grants, refer to the NIH Guide, Volume 25, Number 10, March 29, 1996 and Volume 28, Number 11, March 19, 1999 at the following URL address: http://www.nih.gov/nigms/funding/pa/progproj.html.

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) is interested in supporting projects that improve the capacity of high resolution electron microscopy to study macromolecular assemblies in muscle, bone, cartilage, and skin. Investigators planning to apply for program project grants from NIAMS should consult NIAMS program staff. Guidelines for NIAMS program projects can be found at:
http://www.nih.gov/niams/grants/Guidelines/guidelines.htm

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) is interested in supporting projects that improve the capacity of high resolution electron microscopy to study macromolecular assemblies (receptors and components of signaling pathways) in organs and endocrine tissues of interest to NIDDK and in cellular processes pertinent to NIDDK-relevant diseases including diabetes, kidney and liver diseases.

For details of the SBIR and STTR application and review procedures, consult the combined Omnibus Solicitation of the NIH, CDC, and FDA for SBIR and STTR grant applications. This document is available at http://grants.nih.gov/grants/funding/sbir.htm.

RESEARCH OBJECTIVES

Background

In April 1998, a special Cell Biology and Biophysics Subcommittee of the National Advisory General Medical Sciences Council examined research trends in the areas of molecular cell biology, structural biology and biophysics. Among the challenges and opportunities identified by the panel were better methods for structural analysis of large macromolecular assemblies and for imaging macromolecules in cells. In November 1998, NIGMS and the National Center for Research Resources (NCRR) convened a workshop to evaluate issues of instrumentation and technology development for high resolution EM.

The workshop participants noted that to achieve a molecular understanding of higher order cellular processes, information about cellular dynamics from light microscopy must be interfaced with atomic-level structural information about isolated components. There are gaps in our abilities to make this connection because many important processes are mediated by macromolecular assemblies that are too large or too variable in structure to solve by X-ray

crystallography and NMR. Biological structure on this scale is approachable by high resolution EM, applied in conjunction with other structural techniques. However, EM technology is underdeveloped as a practical tool for routine, high-throughput application in this role.

The panel emphasized that improved EM capabilities for direct visualization of macromolecular arrangements in very large assemblies and intact cells are needed. Without them, indirect approaches that are much slower and more expensive will have to be customized for each class of problems. The panel noted that NIH supports a number of projects that apply EM to a broad range of biological problems, but that relatively few projects are directed towards improving EM technology. They emphasized the importance of support for technology development to improve the capabilities of high resolution EM.

In response to the findings and recommendations of the workshop as endorsed by the National Advisory General Medical Sciences Council at its May 1999 meeting, this PA addresses technology development for high resolution EM. An accompanying PA addresses instrumentation needs for high resolution EM.

Scientific Objectives

The goal of this PA is to promote technology development for high resolution EM.

The objectives of this PA are to:

o Automate and increase the throughput of proven methods for intermediate and high-resolution structure analysis of frozen-hydrated arrays and symmetrical particles.

o Develop the capability to determine atomic resolution structures of large, isolated, frozen-hydrated macromolecular assemblies in solution, eliminating current dependence upon specimen periodicity.

o Develop the proven technology of 3-D cellular tomography of fixed, embedded, and sectioned specimens as a routine, high-throughput structural tool.

o Develop approaches for determining 3-D macromolecular arrangements in native cells, for example, by matching electron image data from thin cryo-sections of cells with the known atomic structures of isolated components.

Scope

The field of high resolution EM has advanced to the stage where major efforts to improve technology are needed for the next steps forward. There is a particular need to increase throughput and reduce dependence on highly skilled personnel. This can be accomplished by developing automated capabilities in the most labor- and skill-intensive aspects of EM. These efforts will require interdisciplinary approaches and collaboration between microscopists and experts in the fields of engineering, physics, mathematics, computer science, chemistry, and materials science. Investigator-initiated research grant applications are invited for the following efforts:

1. The development of improved reagents, methods, instrumentation, algorithms, software, and automation.

o For conventionally embedded specimens, needs include: better reagents and automated methods for rapid freezing (to freeze native structure and transient processes), preservation, staining, embedding, sectioning, and the specific labeling and detection of macromolecules in cells.

o For high resolution EM of frozen hydrated specimens, improvements in instrumentation for cryo-specimen preparation are needed to improve reproducibility and control. Automation is needed to increase throughput and to make the technology accessible to less highly skilled personnel.

o To reduce signal loss and achieve improvements in resolution, attention is needed to specimen-beam interactions, stage design, electron optics, and detector technology.

o For high-throughput data collection, needs are: automated, intelligent microscope operation, interactive remote microscope control, and high-speed data acquisition.

o For data processing, new approaches are needed for high-throughput data management, image analysis (algorithms and software for classification, pattern recognition, knowledge-based methods), interpretation of results (model building, interactive visualization and display), and control (accessible, efficient user interfaces).

o In all areas, there is a need for methods, tools and standards for benchmarking the performance of instruments and software.

Workshops, Conferences, and Courses.

The participating institutes are particularly interested in supporting outreach activities to foster collaboration among experts in the fields of engineering, physics, mathematics, computer science, chemistry, and materials science, as well as activities to promote coordination between research groups on developing standards and benchmarks. Potential applicants should contact staff (see Inquiries below).

Summary

This PA is intended to provide investigators applying EM to problems in molecular cell biology with better technology and methods for structural analysis of large macromolecular assemblies and for imaging macromolecules in cells. Research projects responding to this PA should significantly advance in a general way the capabilities of EM for (1) determination of the atomic structures of isolated macromolecular assemblies or (2) the analysis of the spatial distribution of macromolecules in cells.

INCLUSION OF WOMEN AND MINORITIES IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of the NIH that women and members of minority groups and their subpopulations must be included in all NIH supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification is provided that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. This policy results from the NIH Revitalization Act of 1993 (Section 492B of Public Law 103-43).

All investigators proposing research involving human subjects should read the "NIH Guidelines For Inclusion of Women and Minorities as Subjects in Clinical Research," which have been published in the Federal Register of March 28, 1994 (FR 59 14508-14513) and in the NIH Guide for Grants and Contracts, Vol. 23, No. 11, March 18, 1994 available on the web at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not94-100.html

INCLUSION OF CHILDREN AS PARTICIPANTS IN RESEARCH INVOLVING HUMAN SUBJECTS

It is the policy of NIH that children (i.e., individuals under the age of 21) must be included in all human subjects research, conducted or supported by the NIH, unless there are scientific and ethical reasons not to include them.

This policy applies to all initial (Type 1) applications submitted for receipt dates after October 1, 1998.

All investigators proposing research involving human subjects should read the "NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects" that was published in the NIH Guide for Grants and Contracts, March 6, 1998, and is available at the following URL address: http://grants.nih.gov/grants/guide/notice-files/not98-024.html

Investigators also may obtain copies of these policies from the program staff listed under INQUIRIES. Program staff may also provide additional relevant information concerning the policy.

APPLICATION PROCEDURES

Applications are to be submitted on the grant application form PHS 398 (rev. 4/98) and will be accepted at the standard application deadlines as indicated in the application kit. Application kits are available at most institutional offices of sponsored research and may be obtained from the Division of Extramural Outreach and Information Resources, National Institutes of Health, 6701 Rockledge Drive, MSC 7910, Bethesda, MD 20892-7910, telephone 301/435-0714, email: GrantsInfo@nih.gov.

Applicants planning to submit an investigator-initiated new (type 1), competing continuation (type 2), competing supplement, or any amended/revised version of the preceding grant application types requesting $500,000 or more in direct costs for any year are advised that he or she must contact the Institute or Center (IC) program staff before submitting the application, i.e., as plans for the study are being developed. Furthermore, the applicant must obtain agreement from the IC staff that the IC will accept the application for consideration for award. Finally, the applicant must identify, in a cover letter sent with the application, the staff member and Institute or Center who agreed to accept assignment of the application.

This policy requires an applicant to obtain agreement for acceptance of both any such application and any such subsequent amendment. Refer to the NIH Guide for Grants and Contracts, March 20, 1998 at http://grants.nih.gov/grants/guide/notice-files/not98-030.html

Individual Research Project (R01) Grants Requesting Less Than $250,000 Direct Costs Per Year.

For the R01 mechanism, specific application instructions have been modified to reflect "MODULAR GRANT" and "JUST-IN-TIME" streamlining efforts being examined by the NIH. Complete and detailed instructions and information on Modular Grants can be found at http://grants.nih.gov/grants/funding/modular/modular.htm

R01 applications that request more than $250,000 direct costs per year should follow the instructions in the PHS Form 398.

The title and number of the program announcement must be typed on line 2 of the face page of the application form and the YES box must be marked.

Submit a signed, typewritten original of the application, including the Checklist, and five signed photocopies in one package to:

CENTER FOR SCIENTIFIC REVIEW
NATIONAL INSTITUTES OF HEALTH
6701 ROCKLEDGE DRIVE, ROOM 1040, MSC 7710
BETHESDA, MD 20892-7710
BETHESDA, MD 20817 (for express/courier service)

SPECIFIC INSTRUCTIONS FOR MODULAR GRANT APPLICATIONS

The modular grant concept establishes specific modules in which direct costs may be requested as well as a maximum level for requested budgets. Only limited budgetary information is required under this approach. The just-in-time concept allows applicants to submit certain information only when there is a possibility for an award. It is anticipated that these changes will reduce the administrative burden for the applicants, reviewers and Institute staff. The research grant application form PHS 398 (rev. 4/98) is to be used in applying for these grants, with the modifications noted below.

BUDGET INSTRUCTIONS

Modular Grant applications will request direct costs in $25,000 modules, up to a total direct cost request of $250,000 per year. (Applications that request more than $250,000 direct costs in any year must follow the traditional PHS 398 application instructions.) The total direct costs must be requested in accordance with the program guidelines and the modifications made to the standard PHS 398 application instructions described below:

PHS 398

o FACE PAGE: Items 7a and 7b should be completed, indicating Direct Costs (in $25,000 increments up to a maximum of $250,000) and Total Costs [Modular Total Direct plus Facilities and Administrative (F&A) costs] for the initial budget period. Items 8a and 8b should be completed indicating the Direct and Total Costs for the entire proposed period of support.

o DETAILED BUDGET FOR THE INITIAL BUDGET PERIOD - Do not complete Form Page 4 of the PHS 398. It is not required and will not be accepted with the application.

o BUDGET FOR THE ENTIRE PROPOSED PERIOD OF SUPPORT - Do not complete the categorical budget table on Form Page 5 of the PHS 398. It is not required and will not be accepted with the application.

o NARRATIVE BUDGET JUSTIFICATION - Prepare a Modular Grant Budget Narrative page. (See http://grants.nih.gov/grants/funding/modular/modular.htm for sample pages.) At the top of the page, enter the total direct costs requested for each year. This is not a Form page.

o Under Personnel, List key project personnel, including their names, percent of effort, and roles on the project. No individual salary information should be provided. However, the applicant should use the NIH appropriation language salary cap and the NIH policy for graduate student compensation in developing the budget request.

For Consortium/Contractual costs, provide an estimate of total costs (direct plus facilities and administrative) for each year, each rounded to the nearest $1,000. List the individuals/organizations with whom consortium or contractual arrangements have been made, the percent effort of key personnel, and the role on the project. Indicate whether the collaborating institution is foreign or domestic. The total cost for a consortium/contractual arrangement is included in the overall requested modular direct cost amount. Include the Letter of Intent to establish a consortium.

Provide an additional narrative budget justification for any variation in the number of modules requested.

o BIOGRAPHICAL SKETCH - The Biographical Sketch provides information used by reviewers in the assessment of each individual's qualifications for a specific role in the proposed project, as

well as to evaluate the overall qualifications of the research team. A biographical sketch is required for all key personnel, following the instructions below. No more than three pages may be used for each person. A sample biographical sketch may be viewed at: http://grants.nih.gov/grants/funding/modular/modular.htm

- Complete the educational block at the top of the form page;
- List position(s) and any honors;
- Provide information, including overall goals and responsibilities, on research projects ongoing or completed during the last three years.
- List selected peer-reviewed publications, with full citations;

o CHECKLIST - This page should be completed and submitted with the application. If the F&A rate agreement has been established, indicate the type of agreement and the date. All appropriate exclusions must be applied in the calculation of the F&A costs for the initial budget period and all future budget years.

o The applicant should provide the name and telephone number of the individual to contact concerning fiscal and administrative issues if additional information is necessary following the initial review.

REVIEW CONSIDERATIONS

Applications will be assigned on the basis of established PHS referral guidelines. Applications will be evaluated for scientific and technical merit by an appropriate scientific review group convened in accordance with the standard NIH peer review procedures. As part of the initial merit review, all applications will receive a written critique and undergo a process in which only those applications deemed to have the highest scientific merit, generally the top half of applications under review, will be discussed, assigned a priority score, and receive a second level review by the appropriate national advisory council or board.

Review Criteria

The goals of NIH-supported research are to advance our understanding of biological systems, improve the control of disease, and enhance health. In the written comments reviewers will be asked to discuss the following aspects of the application in order to judge the likelihood that the proposed research will have a substantial impact on the pursuit of these goals. Each of these

criteria will be addressed and considered in assigning the overall score, weighting them as appropriate for each application. Note that the application does not need to be strong in all categories to be judged likely to have major scientific impact and thus deserve a high priority score. For example, an investigator may propose to carry out important work that by its nature is not innovative but is essential to move a field forward.

(1) Significance: Does this study address an important problem? If the aims of the application are achieved, how will scientific knowledge be advanced? What will be the effect of these studies on the concepts or methods that drive this field?

(2) Approach: Are the conceptual framework, design, methods, and analyses adequately developed, well-integrated, and appropriate to the aims of the project? Does the applicant acknowledge potential problem areas and consider alternative tactics?

(3) Innovation: Does the project employ novel concepts, approaches or methods? Are the aims original and innovative? Does the project challenge existing paradigms or develop new methodologies or technologies?

(4) Investigator: Is the investigator appropriately trained and well suited to carry out this work? Is the work proposed appropriate to the experience level of the principal investigator and other researchers (if any)?

(5) Environment: Does the scientific environment in which the work will be done contribute to the probability of success? Do the proposed experiments take advantage of unique features of the scientific environment or employ useful collaborative arrangements? Is there evidence of institutional support?

In addition to the above criteria, in accordance with NIH policy, all applications will also be reviewed with respect to the following:

o The adequacy of plans to include both genders, minorities and their subgroups, and children as appropriate for the scientific goals of the research. Plans for the recruitment and retention of subjects will also be evaluated.

o The reasonableness of the proposed budget and duration in relation to the proposed research.

o The adequacy of the proposed protection for humans, animals or the environment, to the extent they may be adversely affected by the project proposed in the application.

The initial review group will also examine the provisions for the protection of human subjects and the safety of the research environment.

Additional scientific/technical merit criteria specific to the objectives of the PA are included. The initial review group will receive copies of this Program Announcement, and be informed of the intent to promote the development of high resolution EM. For the research component of applications, reviewers will apply the standard NIH review criteria (explained above). For technology development, reviewers will also consider the points below:

o Where the goals of the project or individual aims are to improve methods, the impact may be indirect. The reviewers will be asked to evaluate significance according to the expected impact of the technology on progress in the field, including the breadth and importance of its potential applications.

o Where the aims are to improve methods, the reviewers will be asked to evaluate general usefulness, including the range of biological problems to which the technology will be applicable, its adaptability for practical use, and its accessibility to other investigators. How will the investigator(s) test the effectiveness of the technology in real world applications? What are the provisions to facilitate use by other investigators of the products of the project (for example software portability and compatibility, access to algorithms, source code, instrument design parameters)?

o Reviewers will be informed that investigators from fields not traditionally funded by NIH have been encouraged to apply, especially in collaboration with established, NIH-funded investigators who are already active in the application of high resolution EM to biological problems. Do the investigators have established credentials in their areas of expertise, and are these appropriate for their roles? Are appropriate collaborations in place?

AWARD CRITERIA

Applications will compete for available funds with all other approved applications. The following will be considered in making funding decisions: quality of the proposed project as determined by peer review, availability of funds, and program priority.

INQUIRIES

Inquiries are encouraged. The opportunity to clarify any issues or questions from potential applicants is welcome.

Direct inquiries regarding programmatic issues to:

James F. Deatherage, Ph.D.
Division of Cell Biology and Biophysics
National Institute of General Medical Sciences
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Bethesda, MD 20892-6200
Telephone: (301) 594-3828
Fax: (301) 480-2004
Email: deatherj@nigms.nih.gov

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National Institute of Arthritis and Musculoskeletal and Skin Diseases
45 Center Drive, MSC 6500
Bethesda, MD 20892-6500
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Fax: (301) 480-4543
Email: richard_w_lymn@nih.gov

Sheryl M. Sato, Ph.D.
Director of Cellular Basis of Metabolic Diseases Program
Division of Diabetes, Endocrinology & Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases
Natcher Building, Room 5AN-18J
45 Center Drive, MSC 6600
Bethesda, MD 20892-6600
Telephone: (301) 594-8811
Fax: (301) 480-3503
Email: satos@extra.niddk.nih.gov

Direct inquiries regarding fiscal matters to:

Ms. Phyllis Y. Smith
Grants Management Office
National Institute of General Medical Sciences
Building 45, Room 2AN.55H
Bethesda, MD 20892-6200
Telephone: (301) 594-5243
Fax: (301) 480-2554
Email: finchp@nigms.nih.gov

Mr. Ephraim Johnson
Grants Management Specialist
Grants Management Branch
Division of Extramural Activities
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AUTHORITY AND REGULATIONS

This program is described in the Catalog of Federal Domestic Assistance No. 93.821 for NIGMS, No. 93.846 for NIAMS, and Nos. 93.847 and 93.865 for NIDDK. Awards are made under authorization of sections 301 and 405 of the Public Health Service Act as amended (42 USC 241

and 284) and administered under NIH grants policies and Federal Regulations 42 CFR 52 and 45 CFR Parts 74 and 92. This program is not subject to the intergovernmental review requirements of Executive Order 12372 or Health Systems Agency review.

The PHS strongly encourages all grant and contract recipients to provide a smoke-free workplace and promote the non-use of all tobacco products. In addition, Public Law 103-227, the Pro-Children Act of 1994, prohibits smoking in certain facilities (or in some cases, and portion of a facility) in which regular or routine education, library, day care, health care or early childhood development services are provided to children. This is consistent with the PHS mission to protect and advance the physical and mental health of the American people.

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